The tandem Claisen rearrangement in the construction of building blocks for supramolecular chemistry

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The tandem Claisen rearrangement is a simple but highly efficient reaction to synthesize useful building blocks for supramolecular chemistry. It provides in one step two new C–C bonds in very high yield. The scope and limits of this reaction will be discussed in this review and it will be shown, how macrocyclic compounds as well as rotaxanes or helicates can be formed by use of butenylidene bridged aromatic compounds obtained after the rearrangement reaction. Special aspects will cover the search for new receptors and sensors or for energy transfer properties. The contents of this *tutorial review* are within the field of preparative organic synthesis but in addition cover aspects of inorganic and supramolecular chemistry.

1. Introduction

Supramolecular chemistry is, as defined by J.-M. Lehn, the "chemistry of the non-covalent bond" or the "chemistry beyond the molecule". This means, that it deals with non-covalent interactions between two or more molecules (*e.g.* electrostatic interactions, π–π interactions, hydrogen bonding, ...). In supramolecular chemistry, metal coordination (although it often is highly covalent in nature) is also considered as "non-covalent" due to the reversibility of the bond formation and the thermodynamic control of the assembly processes.

Molecular recognition phenomena play an important role in supramolecular chemistry to achieve the specific assembly of only one well defined ensemble. If the formation of the aggregate proceeds spontaneous and eventually cooperative we term it "self-assembly".[1]

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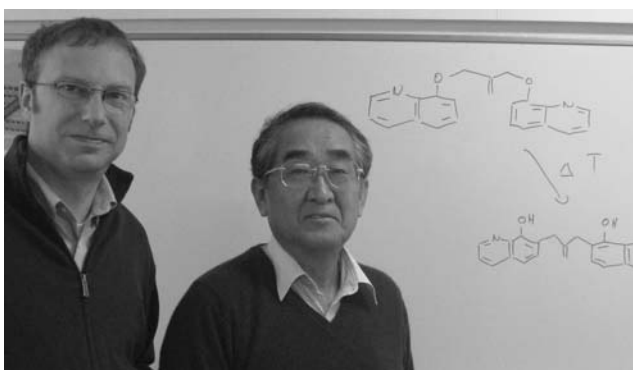
During the last 40 years receptors with high specificity and selectivity have been designed and prepared, and building blocks for huge aggregates have been obtained in rational approaches. Hereby, metal coordination and metallosupramolecular chemistry afforded a high diversity of different structures based on the symmetry of the ligands as well as on the preferred coordination geometry of the metals. This could be used to obtain new receptors and to generate supramolecular reaction centers.[2]

However, each of the studies to obtain receptors or self-assembled aggregates starts with the preparation of molecular building blocks. This synthesis is often complicated and may yield only minor amounts of material. Therefore, new synthetic techniques and protocols for the practicable synthesis of building blocks are needed. The Claisen rearrangement can be used as a simple reaction to introduce C–C bonds and OH groups.[3] In the tandem Claisen rearrangement version, as introduced by Hiratani, two C–C bonds can be formed simultaneously (see Scheme 1) and novel receptors having two OH groups as well as building blocks can be obtained.[4]

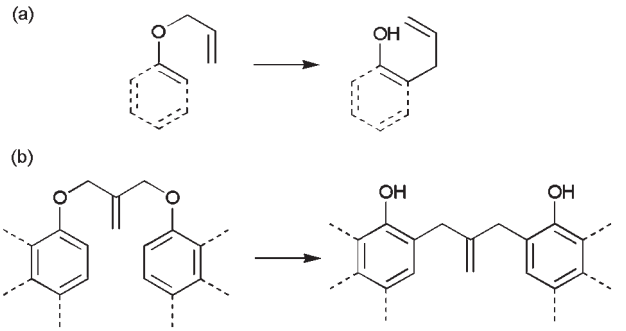
This review introduces the tandem Claisen rearrangement for the synthesis of supramolecular building blocks either as



Markus Albrecht and Kazuhisa Hiratani

Kazuhisa Hiratani was born in 1945 in Hiroshima. He studied chemistry at the Tokyo Institute of Technology and received his doctoral degree of chemistry in 1974 (Prof. M. Okawara). Between 1974 and 2001 he was researcher at a national institute and in 1977/78 he was Alexander von Humboldt fellow at the FU Berlin (with Prof. G. Manecke). Since 2001 he is full-professor of applied chemistry at the Utsunomiya University.

Markus Albrecht was born in 1964. He studied Chemistry in Würzburg and Münster and obtained his Dr rer. nat. in 1992 (Prof. G. Erker). After one year as a postdoctoral fellow with Prof. K. N. Raymond in Berkeley he moved to the University of Karlsruhe and received his habilitation in 1997. Since Spring 2002 he is professor of Organic Chemistry at the RWTH-Aachen.



Scheme 1 Comparison of the Claisen rearrangement (a) and the double- or tandem-Claisen rearrangement reaction as introduced by Hiratani (b).

receptors or as ligands. Selected examples for the rearrangement reaction and its application for receptor synthesis are presented and their supramolecular chemistry is illustrated.

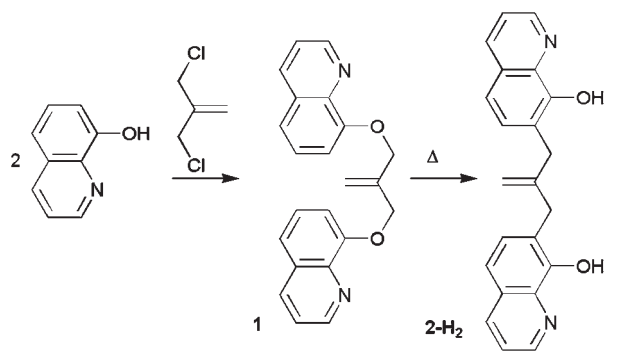
2. The tandem Claisen rearrangement

Scheme 1 presents the Claisen (a) as well as the tandem Claisen (b) rearrangement reaction. In the latter case a two-step reaction proceeds stepwise and allows the successive formation of two new C–C bonds. Usually this reaction proceeds without solvent in very high yield (quantitatively) under thermal conditions (160–190 °C).[4] However, if those reaction conditions are too harsh, it can be performed in high boiling solvents[5] or at room temperature under Lewis-acid catalysis (*e.g.* Et_2AlCl).[6]

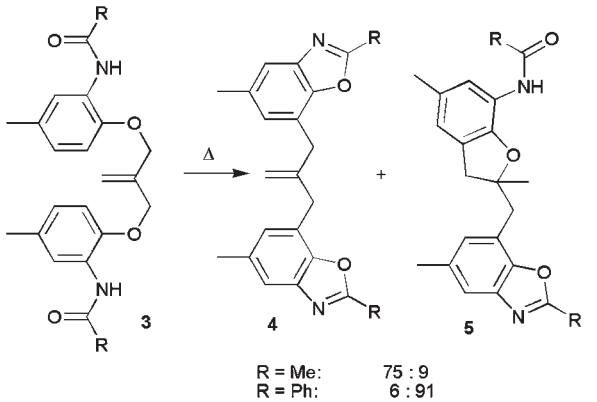
In 1995 the first examples for the tandem Claisen rearrangement reaction were reported. For instance, reaction of 8-hydroxyquinoline with 3-chloro-2-chloromethylpropene led to the diether **1** which under thermal conditions was rearranged to the isobutenylidene bridged compound **2-H$_2$** (Scheme 2).[4,7]

Several more examples for this rearrangement reaction were described.[4] Following this work, computational and structural investigations were performed which showed the preferred conformation of the isobutenylidene unit bridging two aromatic ring systems.[8]

If the tandem Claisen rearrangement was performed under thermic conditions starting from diether **3** (which was obtained from 2-amidophenol), bis(benzoxazoles) **4** were obtained as the major products. However, in some cases



Scheme 2 Tandem Claisen rearrangement leading to the isobutenylidene bridged bis(8-hydroxyquinoline) **2**-H$_2$.



Scheme 3 Preparation of bis(benzoxazoles) **4** by tandem Claisen rearrangement.

(*e.g.* when R = Ph) the cyclization product **5** became dominant (Scheme 3).[5]

Compounds **4** were highly fluorescent[9] and they could be incorporated into polymers by performing the tandem Claisen rearrangement with polyamides using compounds such as **3** as a monomeric diamine in the preparation of the polymers.[10]

3. Building blocks for supramolecular chemistry

As already mentioned, the tandem Claisen rearrangement reaction represents an attractive approach towards the simultaneous introduction of two new C–C bonds. Furthermore, two phenolic units are generated. Those can be used for functionalization or for the coordination of metal ions and thus novel receptors can be envisaged. If the isobutylenylidene unit is part of a ring system, the rearrangement alters the ring geometry and size.

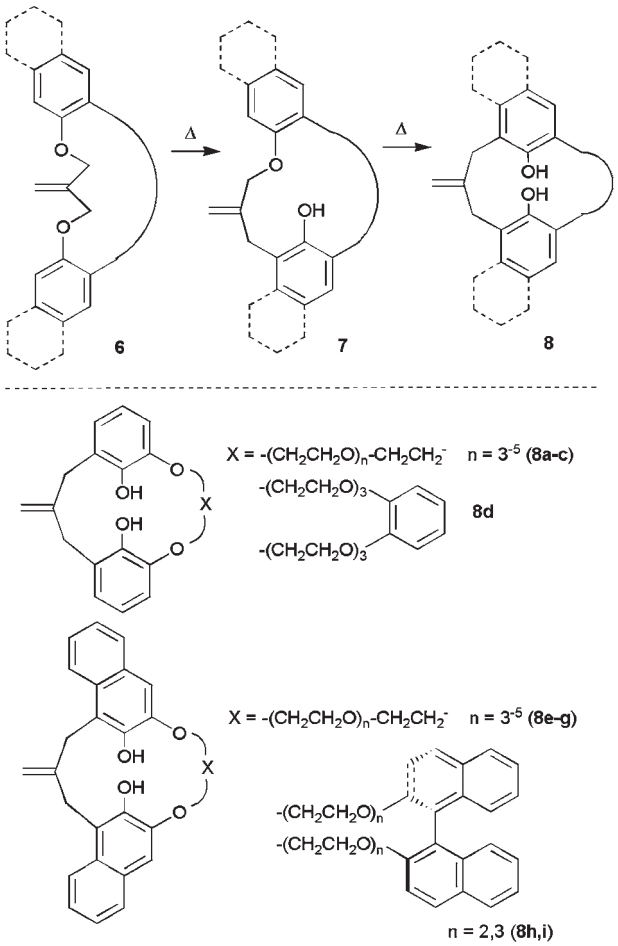
In this section, examples for the synthesis of novel macrocyclic compounds which act as receptors towards small cations, anions or neutral molecules are discussed. Consequently this approach leads to a new synthesis of rotaxanes. Finally, the coordination chemistry of linear receptor type derivatives is described, in which template directed self-assembly of helicates is achieved and enables the formation of heterodinuclear functional helicates which act as sensors or possess some energy transfer properties.

3.1. Macrocycles

Incorporation of the isobutenylidene diaryl ether in a ring system allowed the preparation of macrocycles, which after rearrangement bore hydroxy groups. These could be used as functional groups for host–guest chemistry or for further functionalization.

Following this concept (Scheme 4), a series of catechol or dihydroxynaphthalene derived macrocycles **8** was obtained.[11] In case of **8e–g**, intermediates **7e–g** could be isolated depending on the reaction conditions.[12] In **8h** and **8i** 2,2′-binaphthol units are incorporated in the ring. They represent chiral, enantiomerically pure derivatives.[13]

If the polyglycol chain in the ring was not attached to the aromatic unit by an ether linkage but by an amide connection, again the formation of benzoxazoles was observed which are



Scheme 4 Stepwise rearrangement of **6** to initially form intermediate **7**, which further rearranges to **8** (top), and examples of macrocycles **8a–i** which were prepared by this method (bottom).

now incorporated in the macrocycle. The fluorescent properties of such compounds (only **9** is depicted as a representative example in Fig. 1) were thoroughly investigated.[14]

Macrocycles could also be formed by an alternative route. Therefore the tandem Claisen rearrangement was performed with the isobutenylidene ether of salicylic aldehyde followed by imine condensation with diamines.[15] The result of an X-ray

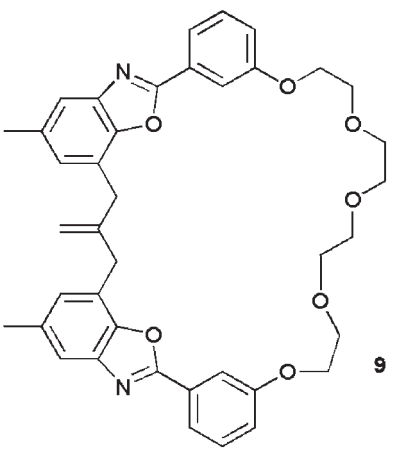


Fig. 1 A macrocyclic fluorescent bis(benzoxazole) **9**.

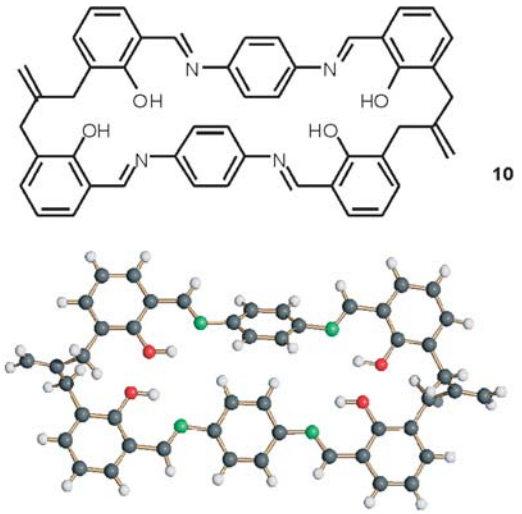


Fig. 2 Crystal structure of macrocycle **10**.

crystal structure analysis of one representative compound **10** formed from the dialdehyde and *p*-phenylenediamine is shown in Fig. 2.[16]

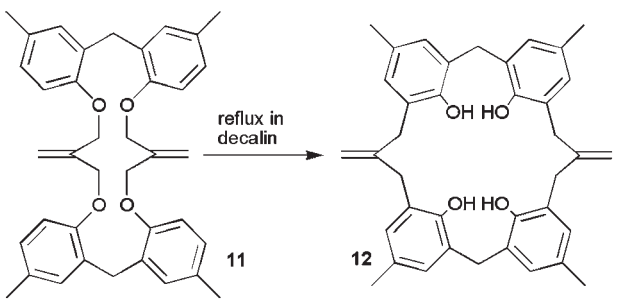
Macrocycles with two diaryl methane units **11** afforded, in a simple two-step procedure after tandem Claisen rearrangement, calixarene analogues **12** in high yields (Scheme 5).[6,17] Calixarene like molecules of this type could then be used for further derivatization as was exemplified by Wang and Gutsche.[18]

Macrocyclic compounds, which were obtained by the tandem Claisen rearrangement, could be used for host–guest chemistry. Sometimes, however, unexpected observations were made; for instance, reaction of the sulfur containing macrocycle **13** with mercury(II) acetate did not lead to simple complexation of the mercury cation to the macrocycle (Scheme 6) but rather an oxymercuration reaction occurred at the isobutenylidene double bond and afforded the organometallic derivative **14**.[19]

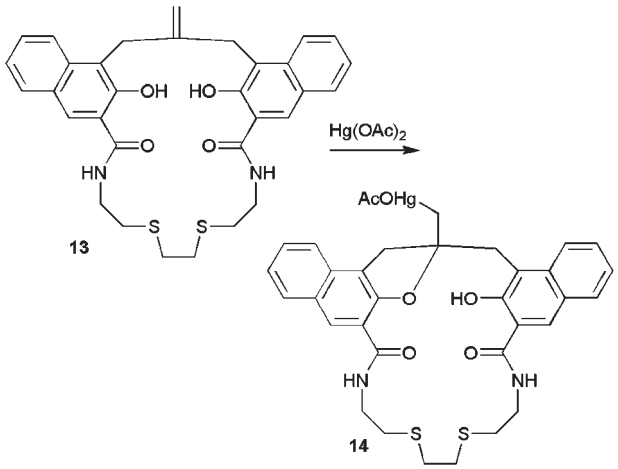
However, in other cases host–guest chemistry proceeded as expected. Thus, the chiral macrocycles **8h,i** (Scheme 4) could bind phenylglycinol, phenylalaninol or phenylethylamine with significant but low stereochemical discrimination.[20]

Macrocycles **8a–c** were found to bind water molecules in the solid state in which the OH groups played an important role as hydrogen bond donors for the binding.[21]

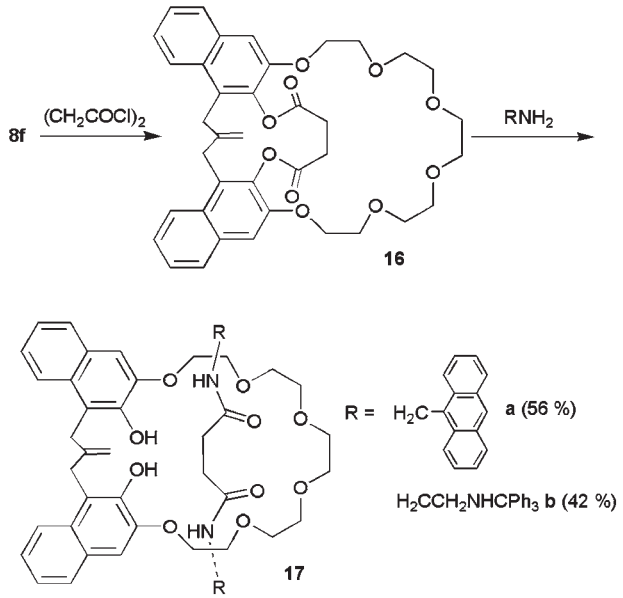
Following this concept, macrocycle **15** (Fig. 3) was specially designed for the fixation of carbon dioxide in its carbonic acid



Scheme 5 Preparation of calixarene analogues **12** by tandem Claisen rearrangement.



Scheme 6 Oxymercuration of the isobutenylidene double bond of **13** to obtain **14**.



Scheme 7 Preparation of rotaxanes **17** *via* tandem Claisen rearrangement (affording **8f**), diesterification and aminolysis.

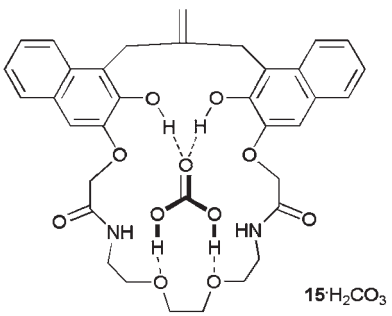


Fig. 3 Binding of CO_2: the host–guest complex **15**·H_2CO_3.

form. The complex **15**·H_2CO_3 was formed at room temperature from a solution of **15** in wet acetonitrile which was saturated with CO_2.[22]

3.2 Rotaxanes

The installation of macrocyclic ring systems with two "inward" directed phenolic units allows the synthesis of rotaxanes and of related topologically interesting molecules.

The macrocycle **8f**, which was obtained by tandem Claisen rearrangement, could be transformed into the macrobicycle **16** by reaction with succinic acid dichloride. Reaction of **16** with amines led to cleavage of the aryl esters and the corresponding amides were formed. However, if bulky amines were used, the first attack afforded a mono amide. For steric reasons the second attack was now favored from the opposite site of the ring system resulting in the rotaxane **17**. The use of 9-aminomethylanthracene yielded the rotaxane **17a** in up to 56% (Scheme 7).[23] Due to different reaction rates of the two aminolysis steps, different amines could be introduced as terminal groups of the axis.

This protocol allowed the preparation of topological chiral rotaxanes (Fig. 4). **18** was prepared by this method and chiral HPLC allowed the separation of the two enantiomers followed by thorough characterization, *e.g.* by CD spectroscopy.[24]

A rotaxane type derivative **23** was obtained as outlined in Scheme 8. Reaction of the amine substituted ring **19** with the

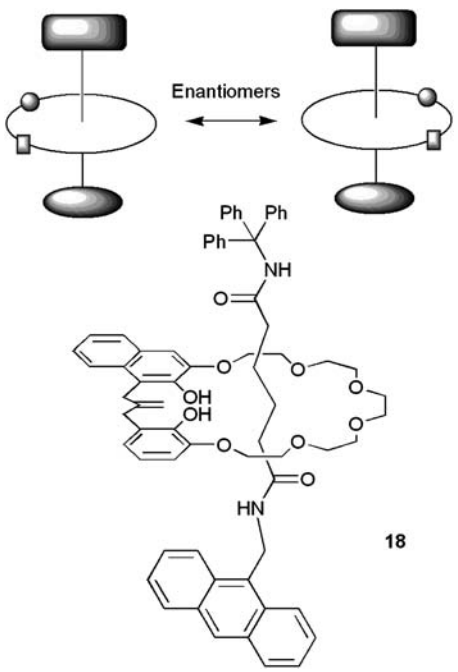
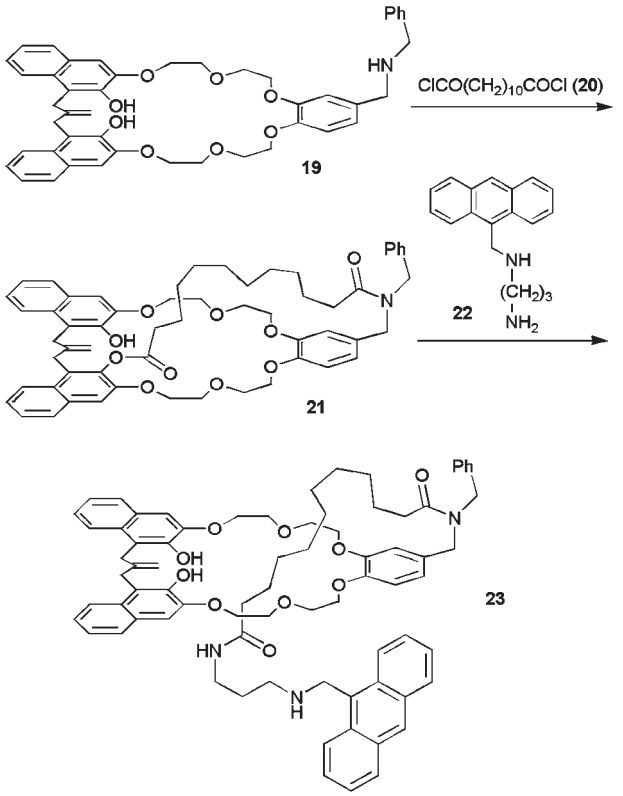


Fig. 4 The chiral rotaxane **18** which could be prepared and resolved into its enantiomers.

diacid dichloride **20** resulted in the formation of the amido ester **21** which by reaction with **22** afforded compound **23** in 45% yield (last step, Scheme 8).

The anthracenyl unit of **23** showed fluorescent properties. Upon addition of lithium ions, the emission was enhanced. This was probably due to binding of the cation to the ring as well as to the "axis" leading to a conformational change which allowed energy transfer from the naphthyl rings (which were excited at 285 nm) to the anthracenyl moiety. This



Scheme 8 Preparation of the rotaxane type compound **23**, which showed unique lithium cation sensing properties.

sensitization is selective for lithium but not for potassium or sodium cations.[25]

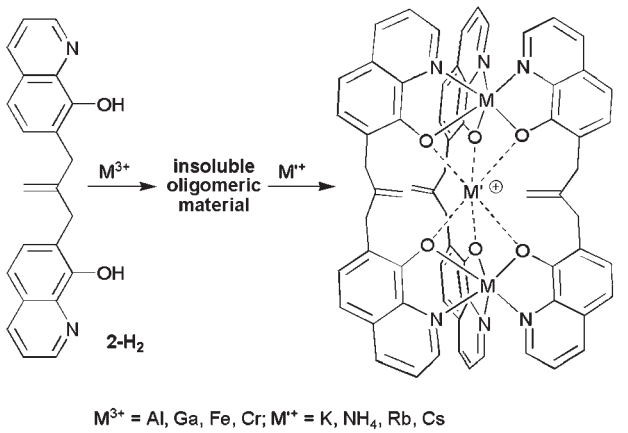
The described results showed, that subsequent functionalization of macrocycles obtained by tandem Claisen rearrangement allowed the preparation of topologically interesting molecules such as rotaxanes. Furthermore it was possible to synthesize chiral rotaxanes and separate the enantiomers as well as develop novel sensors based on the new rotaxane type motif.

3.3 Oligonuclear helicate-type complexes

The tandem Claisen rearrangement opens not only the way to macrocyclic derivatives. Linear compounds are also of interest for the coordination of ions in order to obtain oligonuclear complexes by self-assembly processes.

Homodinuclear complexes. The already described isobutenylidene bridged bis(8-hydroxyquinolinate) derivative **2-H$_2$** seems to be an ideal ligand for the self-assembly of dinuclear complexes with trivalent metal ions.

However, reaction of three equivalents of ligand **2-H$_2$** with two equivalents of metal salts of aluminium, gallium(III), iron(III) or chromium(III) did not result in the formation of well defined species (Scheme 9). A precipitate was formed, which possessed a composition **2** : M of 3 : 2 but consisted of a mixture of oligomeric complexes. Heating of this material in polar solvents in the presence of alkali-metal salts (KCl, RbCl, CsCl) or ammonium chloride resulted in the quantitative transformation of the precipitate into well-soluble dinuclear complexes. Several X-ray crystal structures of such complexes could be obtained, of which a representative example



Scheme 9 Dynamic combinatorial chemistry approach towards the formation of a dinuclear meso-helicate.

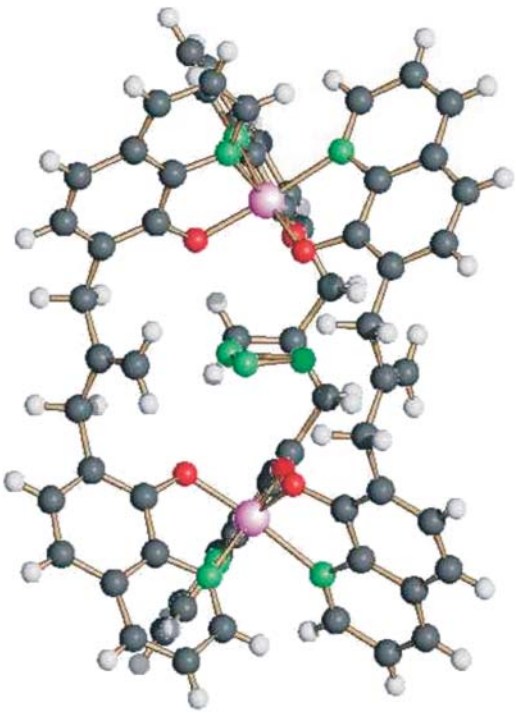


Fig. 5 X-Ray crystal structure analysis of $[(NH_4)\mathbf{2}_3Al_2]^+$. The ammonium ion (green) is disordered over three positions (pink: aluminium).

([$(NH_4)\{\mathbf{2}_3Al_2\}$]Cl) is shown in Fig. 5. The crystal structure analyses revealed the encapsulation of the templating cation in the interior of the triple-stranded complex. Hereby the cation acted as a template which favoured the formation of the dinuclear coordination compound over the formation of the oligomeric material. In addition the meso-relation of the two trisquinolinate metal complex units could be observed from the structural analysis.[26] This was due to the odd number of carbon atoms in the spacer, which led, in case of linear ditopic ligands and (pseudo)octahedral metal complex units, to the observed meso-helicate. Corresponding compounds with an even number of atoms in the spacer resulted in the diastereoselective formation of the chiral helicates as a racemic mixture.[27]

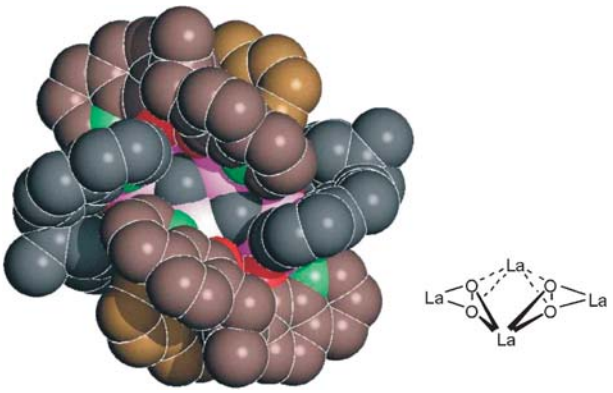
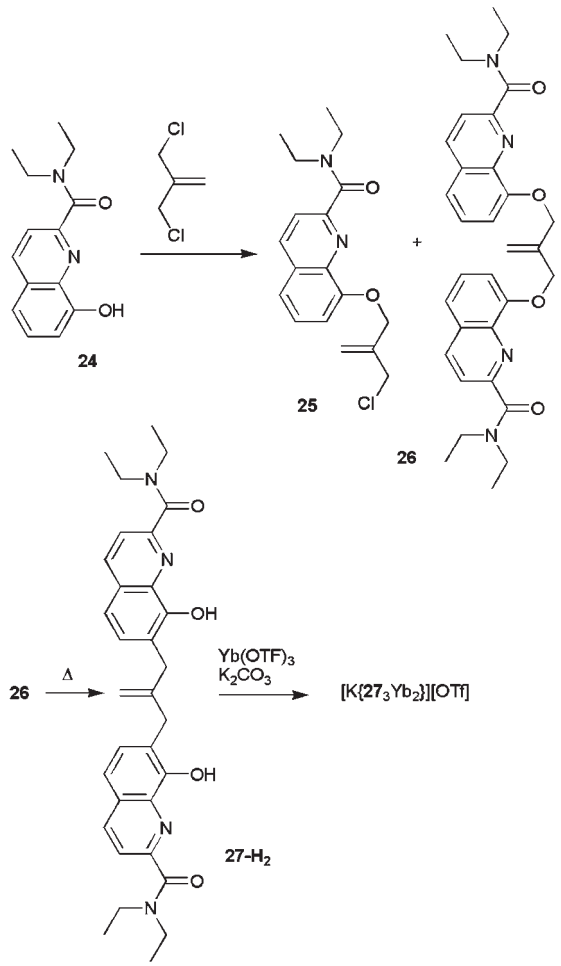


Fig. 6 A tetranuclear lanthanum cluster wrapped up by six ligands **2** as derived from a preliminary crystal structure analysis.

The described template directed formation of the triple stranded meso-helicates of ligand **2** with the formation of oligomeric intermediates is a nice example for the concept of dynamic combinatorial chemistry.

In dynamic combinatorial chemistry, molecular diversity is generated by the formation of a mixture of species which are in a dynamic equilibrium with each other (*e.g.* a mixture of oligomeric compounds). In a subsequent step one (or more) of the species is



Scheme 10 Preparation of the bis-tridentate ligand **27-H$_2$** and its ytterbium complex [K{**27**$_3$Yb$_2$}]OTf.

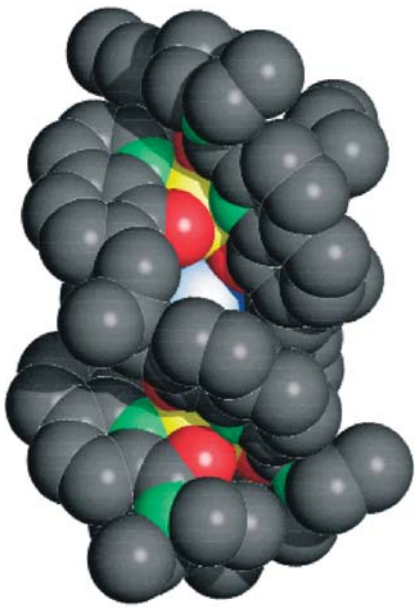


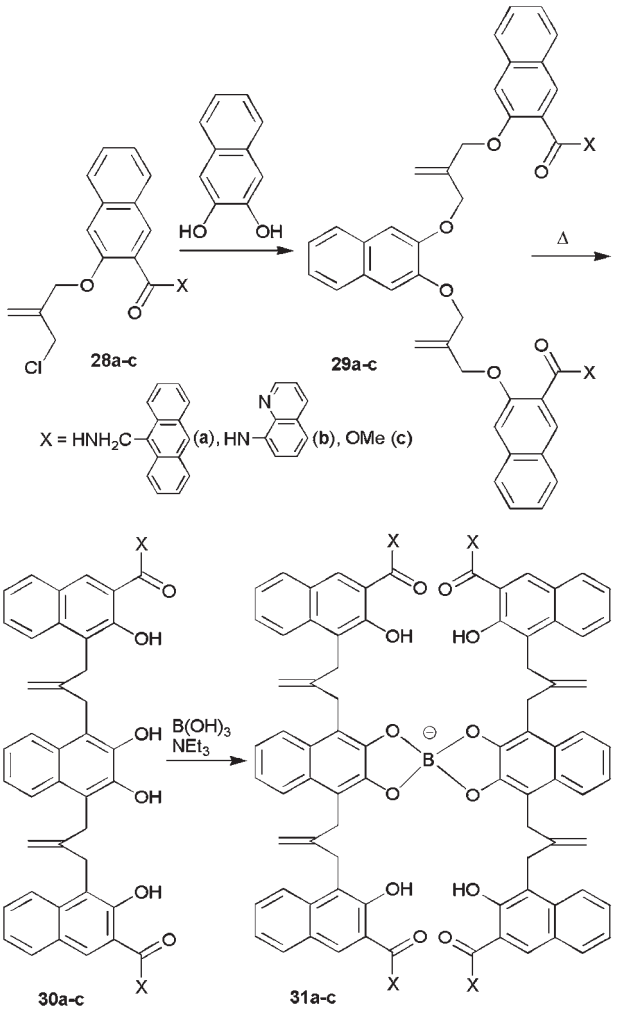
Fig. 7 Crystal structure analysis of [K{**27**$_3$Yb$_2$}]$^+$ with zoom-in on the coordination of the potassium cation (blue: potassium, yellow: ytterbium).

selected by a specific selector (*e.g.* a template). In an ideal case, such as described above (Scheme 9), the whole mixture (dynamic combinatorial library) is transformed into only one species. In the described case it was possible to show this principle nicely, because the intermediate material was neutral and no cations had to be present. Only upon addition of templating cations were the defined coordination compounds formed.[28]

Reaction of the ligand **2** with lanthanum(III) ions in the presence of oxygen afforded a few single crystals. The structure could not be fully resolved (disordered solvent molecules and anions made the satisfactory solution of a final crystal structure impossible). However, a tetrameric lanthanum(III) cluster possessing two O_2^{2-} units could be recognized as central species. The internal $La_4(O_2)_2$ core was wrapped up by six ligands **2** which bridged the metal centers (Fig. 6).[29]

On the other hand, dinuclear helicates with lanthanide(III) ions should be obtained by substituting the bidentate coordination sites of the quinolinates by tridentate 2-amidoquinolinates. The synthesis of the corresponding ligand **27-H$_2$** is shown in Scheme 10.

Ligand **27-H$_2$** was prepared starting from 2-(diethylamido)-8-hydroxyquinoline **24** by coupling with 3-chloro-2-chloromethyl propene to obtain the diether **26** as well as the monoether **25**. The latter could be separated by column chromatography and was also an important synthetic building block (*vide infra*).



Scheme 11 Synthesis of naphthyldiol bis(salicylate) derivatives **30a–c** and their boron complexes **31a–c**.

26 was heated in order to perform the rearrangement reaction and ligand **27-H$_2$** was obtained.[30] Reaction of three equivalents of **27-H$_2$** with two equivalents of ytterbium (or gadolinium) triflate in the presence of potassium carbonate afforded the corresponding triple stranded helicate [K{**27**$_3$Yb$_2$}]OTf.

Although the helicate **27**$_3$Yb$_2$ itself was stable, it could be further stabilized by the binding of an cation in its interior. The X-ray structure (Fig. 7) revealed that potassium was bound to internal oxygen atoms of the quinolinates and in addition this cation seemed to coordinate to one of the vinylic units of the isobutenylidene spacer. However, it could not be deduced from the structural investigation, if this interaction added some significant binding energy.

Three ligands **27** with two terminal tridentate binding sites provided an ideal nonacoordinate environment for the coordination of the two ytterbium cations.[31]

Heterooligonuclear complexes. For the formation of heterooligonuclear coordination compounds ligands bearing two different coordination sites for different metal ions had to be prepared.

Linear molecules with a naphthyldiol and two salicyl-type units were synthesized as outlined in Scheme 11.

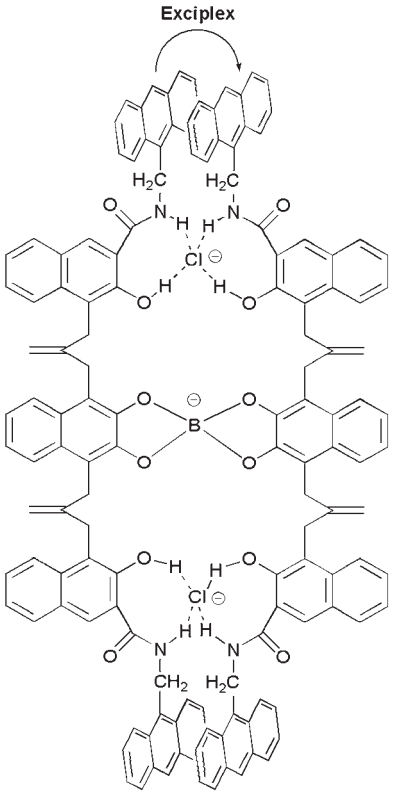


Fig. 8 Binding of chloride ions to an anionic borate complex with fluorescence response upon addition of this anion due to exciplex formation.

The starting materials **28a–c** were prepared from the corresponding salicylic acid derivative (bearing either an anthracenylmethylamide (**a**), quinolinylamine (**b**) or a methyl ester (**c**)) and a large excess of 3-chloro-2-chloromethylpropene. Two equivalents of **28a–c** reacted in a Williamson ether synthesis with 2,3-dihydroxynaphthalene. Rearrangement reactions of **29a–c** proceeded upon heating to 160 °C (75–80%). The obtained compounds **30a–c** with a catechol-type binding site could be coordinated to boron to obtain the anionic double stranded complexes **31a–c** (Scheme 11).

All three compounds **31a–c** possessed additional binding sites for the coordination of ions. Thus, the anthracenyl substituted amide **31a** was used for the fluorescence sensing of anions. Addition of a series of different anions (fluoride, acetate, dihydrogenphosphate, hydrogensulfate, chloride, bromide and iodide) all resulted in a 2 : 1 anion/**31a** complexation. However, only with chloride was a specific response of the fluorescent anthracenyl groups detected. Upon addition of the chloride the typical emission at 412 nm (excitation at 350 nm) decreased, while a strong emission band at 544 nm appeared. This behaviour was assigned to an exciplex formation of the anthracenyl units upon complexation of the chloride ions (Fig. 8).[32]

Using the quinoline derivative **31b** led to high selectivity in the binding of dihydrogenphosphate over other anions. Probably the quinoline units acted as acceptors for hydrogen bonding with the protons of the dihydrogenphosphate anions.[33]

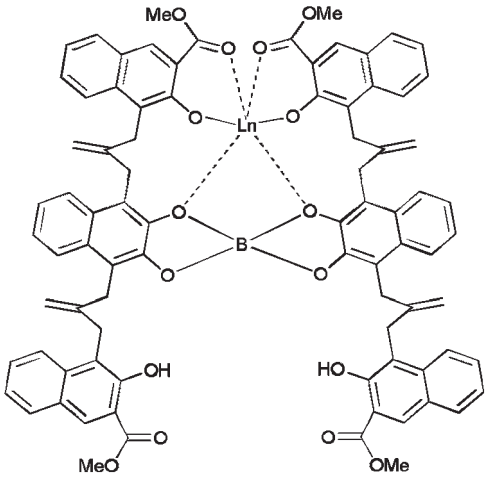


Fig. 9 A heterodinuclear lanthanide(III)–boron complex **31c**·Ln.

The complexes **31a**·$2Cl^-$ and **31b**·$2[H_2PO_4]^-$ represent already heteronuclear double stranded complexes. However, the different centers were one boron and two anions.

In order to introduce metal ions, the ester **31c** was reacted with lanthanide(III) salts. No 2 : 1 (Ln : **31c**) but only 1 : 1 complexes could be obtained, in which one of the lanthanides was bound to terminal salicylic ester units. This coordination probably led to a conformational change and to a structural fixation at the boron, which prevented the coordination of a second lanthanide cation (see Fig. 9).

The stability of the complexes **31c**·Ln (as deduced from spectrophotometric studies) correlated with the size of the lanthanide cations. Small cations were more strongly bound than bigger ones.[34]

A simple unsymmetric bis-8-hydroxyquinoline ligand **32-H$_3$** which possesses one terminal carboxylate unit could be prepared and was reacted with a mixture of lanthanum(III) triflate and zinc acetate in an attempt to obtain a triple stranded heterodinuclear complex. However, only the dinuclear double-stranded zinc complex $[\mathbf{32}_2Zn_2]^{2-}$ could be isolated, in which the two ligands adopted an antiparallel orientation and the zinc cations showed pentacoordination, binding to a bidentate unit of one and the tridentate moiety of the other ligand (Fig. 10).

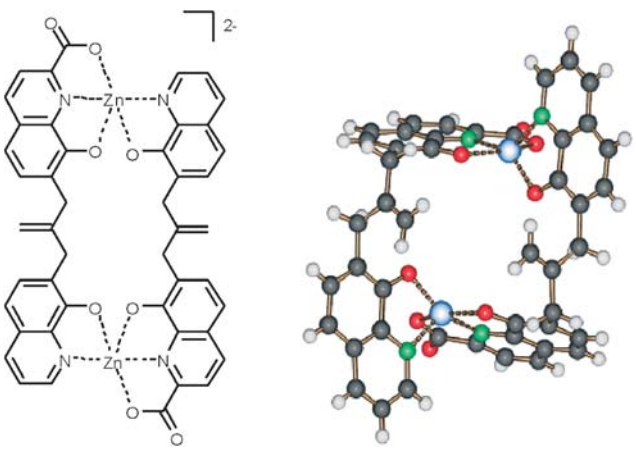
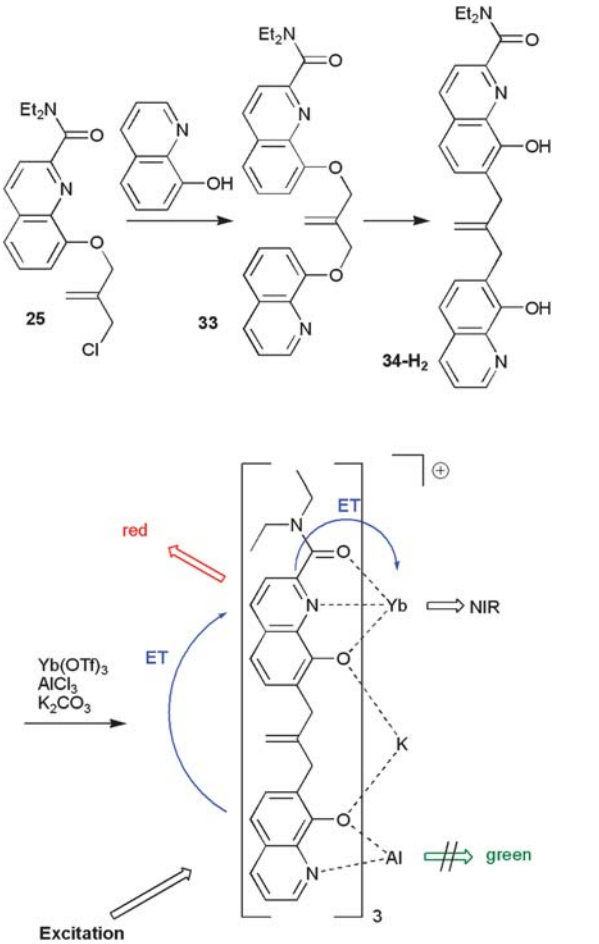


Fig. 10 The dinuclear zinc complex $[\mathbf{32}_2Zn_2]^{2-}$ (blue: zinc).



Scheme 12 Preparation of an unsymmetric ligand **34** and of its heterodinuclear ytterbium(III)–aluminium complex $K\{\mathbf{34}_3YbAl\}]^+$ which shows some intramolecular energy transfer (ET) processes.

The corresponding triple stranded dinuclear lanthanum—zinc complex could probably not be obtained due to the high negative charge at the deprotonated tridentate unit, which would destabilize the lanthanum(III) complex (a charge of 3− would be built up).[35]

In order to get a heterodinuclear complex, the charge at the tridentate unit had to be reduced. Therefore, the amide substituted unsymmetric ligand **34-H$_2$** was prepared using the side-product **25** which was obtained in the reaction presented in Scheme 10. Coupling of **25** with 8-hydroxyquinoline resulted in the formation of the ether **33** which was rearranged to obtain the unsymmetric ligand **34-H$_2$** (Scheme 12).

Reaction of **34-H$_2$** with aluminium trichloride and ytterbium(III) triflate in the presence of potassium carbonate afforded the heterodinuclear complex $[K\{\mathbf{34}_3YbAl\}]^+$. Excitation of this complex at 360 nm did not lead to the green emission which was expected for the aluminium quinolinate unit. Photophysical studies showed an intramolecular quenching process which led to an energy transfer from the aluminium complex unit to the amidoquinolinate ligand and thus enhanced the red emission of this unit and in addition led to an enhanced energy transfer between the amidoquinolinate and the ytterbium cation resulting in higher quantum yields and longer life times for the NIR emission of $K\{\mathbf{34}_3YbAl\}]^+$ compared to $[K\{\mathbf{27}_3Yb_2\}]^+$.[31]

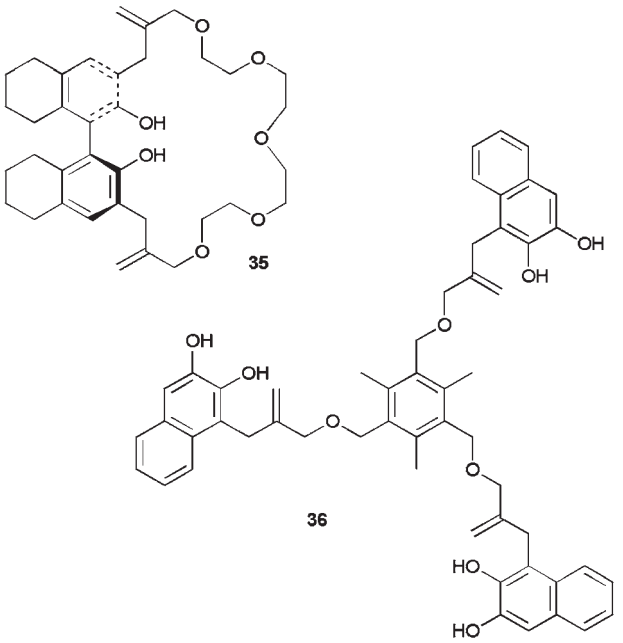


Fig. 11 Further compounds obtained by tandem Claisen type reactions.

4. Conclusion

In this article we have discussed a very simple but highly effective method to introduce isobutenylidene spacers between two phenolic units: the tandem Claisen rearrangement reaction. We presented several examples how this method could be used for the synthesis of linear as well as cyclic derivatives and described the application of the rearranged compounds in supramolecular chemistry, as receptors, rings for rotaxanes or ligands for oligotopic complexes. However, we believe that this reaction, which was introduced in 1995, has a much broader potential and also could be used for, *e.g.*, natural product synthesis or for the preparation of new organic materials (as already indicated in this article).

A further possibility is to extend the method by switching from the isobutenylidene moiety to others with several ''allylic'' units which are able to undergo the Claisen rearrangement. First results in this direction were already obtained, *e.g.*, in the synthesis of enantiomerically pure chiral macrocycles like **35**[36] or of tripodal compounds for the complexation of metal cations like compound **36** (Fig. 11).[37]

The tandem Claisen rearrangement is a simple reaction, which is easily performed and affords products in high yield and high purity.

We hope that we were able to show this aspect here and that others will be inspired by this review in order to use this reaction in different research projects and apply it to different problems.

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